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Review

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A Review of Coronavirus Infection in the Central Nervous System of Cats and Mice

Janet E. Foley and Christian Leutenegger

Feline infectious peritonitis (FIP) is a common cause of death in cats. Management of this disease has been hampered by difficulties identifying the infection and determining the immunological status of affected cats and by high variability in the clinical, pathological, and immunological characteristics of affected cats. Neurological FIP, which is much more homogeneous than systemic effusive or noneffusive FIP, appears to be a good model for establishing the basic features of FIP immunopathogenesis. Very little information is available about the immunopathogenesis of neurologic FIP, and it is reasonable to use research from the well-characterized mouse hepatitis virus (MHV) immune-mediated encephalitis system, as a template for FIP investigation, and to contrast findings from the MHV model with those of FIP. It is expected that the immunopathogenic mechanisms will have important similarities. Such comparative research may lead to better understanding of FIP immunopathogenesis and rational prospects for management of this frustrating disease.

Key words: Cats; Feline infectious peritonitis; Mouse hepatitis virus; Neurological disease.

Feline infectious peritonitis (FIP) is a fatal, immune-mediated disease produced as a result of infection of macrophages by mutant feline coronavirus strains (FIPVs). The severity of FIP is determined by virus strain and by host-specific, partially heritable immune responses.[1] The causative agent, FIP virus (FIPV), is a macrophage-tropic mutant of the ubiquitous feline enteric coronavirus (FECV).[2–4] These feline coronaviruses are closely related to transmissible gastroenteritis virus (TGEV) of pigs and more distantly related to MHV (a coronavirus of rodents), human respiratory coronavirus, and others. As with most RNA viruses, a high rate of point or other small-scale mutations and larger scale recombination events occur. Type II FECVs are viruses that arise as a result of recombinations between type I FECV and canine coronavirus (CCV). Type II FECVs acquired a canine S gene and express a canine S gene product.[5] Mutations are common in the 7b open reading frame (ORF) of both type I and type II FECVs and may be associated with reduced virulence.[4,6] The 7b ORF arose in the FECV/CCV lineage and encodes a nonstructural secretory glycoprotein of undetermined function, which is not necessary for viral replication.[7] Deletions, point mutations, and frame-shift mutations leading to early truncation of the 3c ORF also are common.[4,6] Because FIP-defining mutations may occur in the S, 3c, and 7b genes, polymerase chain reaction (PCR) with these genes as a target cannot discriminate between benign FECV and fatal FIPV.[2–4]

Murine hepatitis virus shares most genes with the FECVs, including M (membrane glycoprotein), E (small membrane), N (nucleocapsid), and S (spike glycoprotein), which is post-translationally modified to S1 and S2.[8] The MHV genome, however, also codes for an HE protein and does not contain a 7b ORF. Mutations in the E and S proteins lead to attenuation of MHV.[9] A third coronavirus, HCV-229E, has been implicated in neurological disease in people.[10]

Clinical Manifestations of Coronaviral Infection in the Central Nervous System (CNS)

FIPV in Cats

FIP occurs most frequently in cats younger than 3 years of age from multiple-cat homes (shelters and breeding catteries).[11,12] One-quarter to one-third of cats with noneffusive FIP have either primary neurological FIP or neurological abnormalities as a part of their overall disease presentation (Foley and Pedersen, unpublished data).[13] The immunological and pathological characteristics of neurological FIP, however, are much more stereotypic than those of systemic FIP. Thus, neurological FIP may be useful for studying basic mechanisms of FIP pathogenesis. The extent to which genetic differences among viral strains confer relative neurotropism is unknown, but some cats with severe neurological disease have mild or undetectable systemic disease.

Both neurological and generalized FIP may present first as a nonspecific illness, with clinical signs including weight loss, weakness, fever, and lethargy. Abdominal abnormalities are detected commonly on physical examination of cats with neurological FIP, including mesenteric lymphadenopathy and irregular splenic and renal surfaces.[14,15] Common historical findings in cats with neurological FIP include dementia, pica, seizures, inappropriate elimination, incontinence (fecal and urinary), and compulsive licking.[15,16] Neurological examination may identify ataxia, hyperesthesia, reduced consciousness, hyperreflexia, crossed-extensor reflexes, reduced conscious proprioception, caudal paresis, cerebellar-vestibular signs, or cranial nerve deficits.[14,15,17–19] Ophthalmic lesions also are common in neurological FIP, including anterior uveitis, keratic precipitates, flocculent debris in the anterior chamber, retinitis, and anisocoria.[15]

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MHV in Mice and Rats

Murine hepatitis virus, like FIPV, can produce either systemic infection or disease primarily affecting the liver. Well-defined neurotropic genetic variants of MHV also occur, including a well-studied variant designated MHV-JHM, which is responsible for progressive encephalomyelitis and death in infected mice and rats. Intranasal or intracranial inoculation of MHV-JHM in BALB/C or C57Bl/6 mice leads to rapid, fatal encephalitis.[20] The syndrome in survivors (either because the virus is attenuated or the host is resistant, vaccinated, or a pup from a vaccinated dams) consists of chronic demyelination and hindlimb paralysis[21] and has been proposed as a model for multiple sclerosis.[22] Determinants of neurovirulence are found in the MHV S gene.[23,24] A second variant of MHV, MHV-OBLV60, leads to neuronal infection specifically in the anterior olfactory bulb after intranasal challenge in mice.[25]

Pathology of Coronavirus-Associated Neurological Disease

FIP Pathology

The definitive lesion of FIP is a pyogranuloma that results from immune-mediated phenomena secondary to coronaviral infection of macrophages. The most common sites are serosal, pleural, meningeal, ependymal, or uveal membranes. In the earliest stages of abdominal FIP, diffuse alterations with activated mesothelial cells and a few coronavirus-infected macrophages or an exudative precipitate may be detected on serosal surfaces.[26] Larger pyogranulomas become grossly visible, ranging from small lesions, often on the renal capsular surface, to severe, generalized miliary granulomatous lesions that distort renal surfaces, disseminate throughout the omentum and gastrointestinal serosa, and invade splenic and hepatic parenchyma. Gross lesions of FIP in the CNS may be subtle, with ependymitis, thickening and opacification of meninges, and ventricular dilatation, usually in the fourth ventricle and least often in the lateral ventricles.[15] Lesions occur most commonly on the ventral surface of the brain, often accompanied by secondary obstructive hydrocephalus.

Histopathologically, lesions in the brains of cats with FIP consist of meningitis, ependymitis (ranging from mild ependymal infiltration to complete effacement of the ependymal lining by a heavy infiltrate of histiocytes and lymphocytes), periventriculitis, and choroiditis of varying severity, often superficial and oriented around the ventricles, with dense infiltrates of lymphocytes, plasma cells, neutrophils, and macrophages.[14,15,27–31] Meningitis may be more severe on the ventrocaudal surfaces of the brain, especially at the base of the cerebellum and the brainstem, including the medulla oblongata. In the meninges, the inflammatory cells may have a predominantly perivascular distribution, forming cuffs around arteries (periarteritis) and infiltrating the wall of veins and venules (phlebitis), with exudation of a cell- and protein-rich edema fluid, and periventricular reactive astrocytosis. The inflammation may extend into the superficial neuropil, as well as into cranial nerve roots.[15] If lesions are deep, they usually are perivascular with scattered glial nodules.[27] Hydrocephalus is seen in association with leptomeningitis, meningeal fibrosis, accumulation of cellular debris, and obstruction of the cerebrospinal fluid flow.

Pathology of Neurotropic MHV

Pathologic lesions after MHV infection in the brains of rats and mice are variable, depending on viral dose and route of administration and rodent genotype, age, and immunological characteristics.[32] In severe acute JHM encephalitis, necrotizing lesions are found in the gray and white matter, with axonal changes, including disintegration of neurofilaments.[32] Within the necrotic areas, perivascular neutrophilic infiltrates occur especially in the subependyma, choroid, and meninges. In acute MHV-A59 infection in CD8+ T-cell deficient mice, periventricular encephalitis occurs with lymphocytic infiltration into the choroid plexus, ependyma, and subependymal brain tissue.[33] Lesions in MHV-OBLV60 consist of local neuronal infection, some mitral cell destruction, and T-cell inflammation with astrocytosis.[25] Some evidence suggests a pathological component of vasculitis, with mouse endothelial cell lines susceptible to MHV-JHM exhibiting cytopathology within several days of infection.[34]

The subacute to chronic immune-modulated pathological changes that occur with manipulation of the MHV-JHM system are particularly relevant to the murine model of FIP. Depending on mouse strain and immunological status, MHV-JHM produces meningeal inflammation associated with T-cells and macrophages and demyelination but relatively little disease in axons. Demyelination occurs within and adjacent to areas of inflammation and astrocytic proliferation.[32,35] Neutrophils and monocytes have been observed infiltrating through endothelial cell junctions and participating in the phagocytosis of myelin debris.[32] Perivascular cuffing by macrophages is observed in chronic encephalitis, as in FIP.

Neurotropic Coronavirus Entry into the CNS and Cell Tropism

FIPV Access and Persistence in the CNS

The route of entry of FIPV into the CNS is unknown. The FIPV virus probably travels hematogenously in macrophages, and 1 study reported a cat with positive immunohistochemical staining for FIPV in monocytes in blood vessels of the choroid plexus.[36] Once in the CNS, there is little evidence that FIPV enters any cells other than macrophages. Foley et al[15] reported positive immunohistochemical staining (by means of a mouse monoclonal antibody against the FIPV N protein) for FIPV, primarily in macrophages in FIP granulomas but also in some lymphocytes. Virus-infected cells were numerous in some areas of intense ependymitis and choroiditis and free within the ventricular lumen, with very few positive cells in the meningeal infiltrates. No staining was observed in vascular basement membranes or in cells of the neuropil. Macrophages in necrotic regions and in the center of lesions often are not infected with coronavirus.[37]

Neurotropic MHV Entry into the CNS

Neurotropic MHV strains have several routes of entry into the CNS. Some studies show that MHV-JHM travels up the olfactory nerve and enters the CNS.[38] This is not surprising, because coronaviruses generally are epitheliotropic, and neurons share embryological origin with epithelial cells. CNS infection with JHM also may occur after peripheral infection and viremia.[39,40] Receptors for neurotropic human coronavirus HCV-229E have been detected not only in human lung cells but also in human neuron, astrocyte, and oligodendrocyte cell cultures.[41] HCV-229E also infects macrophages and endothelial cells, however, suggesting hematogenous introduction into the CNS,[40,42] similar to FIP.

Once inside the CNS, the major targets for MHV are glial cells and neurons.[35] Especially in neuroattenuated strains, MHV-JHM infects primarily oligodendrocytes[43] and has been reported in astrocytes.[44] MHV-4 infects mainly neurons.[20] Subsequent events in chronic disease pathogenesis include recruitment of inflammatory cells and the interactions of immune cells with the virus-infected cells. Macrophages, activated T-cells, and some B-cells may cross into the intact CNS through the blood-brain barrier, with the potential for major cytokine upregulation.[45,46]

The Immunopathogenesis of Neurologic Coronavirus Infections

FIP Immunopathogenesis

After establishment of FIPV in the CNS, mechanisms of disease are primarily immune-mediated, involving humoral and cell-mediated immunity (CMI). Coronavirus-infected macrophages can trigger massive complement activation and deposition of C3 on affected surfaces, disseminated intravascular coagulopathy, vessel necrosis, and effusion.[37,47–49] However, immunopathogenic events in neurological FIP have not been well described.

Antibodies in FIP

Both in systemic and neurological FIP, antibodies (especially to the spike protein) contribute to the opsonization of viral antigen and have the capacity to mediate or enhance disease.[50–54] Antibodies to FECV and FIPV are identical. Anti-FIPV IgG and IgM-producing B-cells are present in FIP lesions, at the interface of healthy tissue and granulomas, and in the serum and CSF of cats with neurological FIP.[26,37] Apparently, some antibody production occurs locally in the CNS, in response to viral antigen in the brain. In one study, serum coronavirus titers of 16 cats with neurological FIP were positive, with a median titer of 1 : 400, whereas CSF titers were positive in 15 cats, with a median titer of 1 : 100.[15] Two cats had high protein concentrations and increased cells, predominantly lymphocytes and neutrophils. The titer in CSF was not statistically correlated with serum titer, and the ratio of serum : CSF titer was not correlated with the serum : CSF protein ratio. If passive leakage of protein from serum into the CSF were invoked to explain the presence of antibodies, it would be expected that the total protein : anti-FIPV IgG ratios would be similar in both serum and CSF. In contrast, CSF IgG titers tended to be proportionally much higher than serum titers. This finding suggests that anti-FIPV IgG may have been produced in the tissues of the brain in response to a locally replicating virus.

FIP Cell-Mediated Immunity and Cytokine Changes

Although almost nothing is known about the mechanism, cell-mediated immunity has been hypothesized to be protective against FIP.[50–54] CD4+ T-cells commonly are observed in FIP granulomas.[37] During acute experimental multisystemic FIP, apoptosis and T-cell depletion were observed in the spleen and mesenteric lymph nodes.[55] This effect was induced by heat-treated effusion fluid (presumably containing some cytokines) but not tissue culture fluid.

Likewise, little is known about the induction of cytokines during the course of FIP. Preliminary findings suggest that development of FIP appears to be associated with a switch to predominantly Th2 immunity, with increases in IL-10 concentrations.[56] Goitsuka et al[57] described increases in IL-6 and IL-1, but Gunn-Moore et al[58] reported reductions in TH_2 and TH_1 cytokines including IL-2, IL-4, IL-10, and IL-12, which they attributed to general immunosuppression. Mildly increased amounts of IL-1α mRNA are detected inconsistently in association with lesions in cells of many organs in cats with FIP.[59] Roles of IL-1 in this setting may include vascular endothelial activation, regulation of macrophages, IL-8 and IL-6, and chemotaxis. IL-6 and IL-1 can increase B-cell growth and differentiation and could exacerbate humoral contributions to the severity of FIP. The inflammatory cytokines TNF-α, IL-1α, and IL-6 could circumvent the blood-brain barrier during systemic FIP, or they could cross the blood-brain barrier after reorganization of the endothelial actin cytoskeleton.[60,61] No information is available regarding cytokine production in neurological FIP, and how cytokines in the CNS compare to those in abdominal tissues of cats with generalized or effusive FIP is unknown.

MHV Immunopathogenesis: Chronic Encephalitis with Demyelination Is an Immune-Mediated Disease

MHV neurological disease can range from severe, acute, necrotizing, rapidly fatal encephalitis to chronic immune-mediated demyelination with little encephalitis, depending on mouse strain, age, and immunocompetence. The appreciation of the principal role of the immune system in producing demyelination emerged from a series of experiments performed over several decades. Profoundly immunosuppressed mice develop high concentrations of virus in the CNS, but demyelination and clinical signs are minimal. Immunocompetent mice have variable or even low concentrations of virus but develop marked disease. Immune reconstitution in immunocompromised mice results in the development of severe demyelinating disease.

If mice are pretreated with passive infusions of antibodies or T-cells or if they receive neuroattenuated MHV strains, they develop chronic, but not fatal, disease after MHV-JHM infection.[62,63] Immunocompetent C57BL/6 mice clear MHV-JHM virus from the brain but develop severe immune-mediated demyelination and paralysis.[22] In contrast, severe combined immunodeficient (SCID) mice have

persistent viral loads but no neurologic impairment or detectable lesions. Gamma-irradiated immunocompromised mice similarly were resistant to chronic demyelination, but reconstitution of the immune system with adoptive transfer of splenocytes restored the immune-mediated lesions.[64]

Cytotoxic T-Lymphocytes (CTLs) and Apoptosis in MHV

Both CD4+ and CD8+ T-cells apparently are required to clear MHV from the CNS. CD8+ T-cells are the predominant infiltrating leukocyte in Lewis rats with MHV-JHM and paralytic disease,[65] whereas infiltration in clinically normal MHV-JHM–positive brown Norway rats consists of CD4+ cells. CTLs may kill some virally infected cells and protect mice from fatal disease, but they do not completely eliminate virus.[66] When CD8+-depleted mice are reconstituted, virus load is reduced, and infection is not detected in most infected cell types, except for oligodendroglial cells.[66] Mice with nucleocapsid or spike protein-specific CD8+ T-cells develop chronic demyelinating disease.[21,67] In the MHV-OBLV60 model, depletion of CD8+ cells is associated with delayed clearance of OBLV60 (but infected mice did recover).[25] CTLs probably exacerbate lesions by contributing to tissue damage. MHV is relatively labile genetically (a common characteristic of RNA viruses), and mutant strains with recognition sites that can evade CTL-mediated viral killing apparently increase and become the predominant viral strains in response to CTL-mediated natural selection. This feature results in disease progression in immunocompetent, but not immunosuppressed, hosts infected with these mutants.[68]

Several studies have suggested that apoptosis may be important in clearing virus from the CNS. Specific CTL recognition promotes apoptosis of MHV-infected cells.[69] In experimental allergic encephalomyelitis in rats, apoptosis appears to help control inflammation.[70]

CD4+ Cells in MHV

The role of CD4+ cells in MHV infection is also complex. Nucleocapsid or spike protein-specific CD4+ T-cells have been shown to protect mice from coronaviral encephalomyelitis in the absence of CD8+ T-cells.[71] If mice with MHV-OBLV60 had CD8+ but not CD4+ cells, they developed persistent infection. If they were CD8+ deficient, but CD4+ cells were normal, they had delayed clearance of the virus, suggesting a primary role for CD4+ cells in clearing this virus.[25] Sussman et al[72] and Williamson and Stohlman[73] documented the requirement for CD4+ cells for clearance of JHM from mice. However, γ-irradiated mice that were reconstituted with CD4+ cells responded to MHV-JHM challenge with earlier and more severe onset of neurological disease.[74] CD4+ knockout mice had less inflammation (with fewer macrophages and microglial cells) and less demyelination than did CD4+ competent mice.[75]

Cytokine Changes in MHV

The presence of MHV-JHM in astrocytes triggers a cytokine cascade that contributes to demyelination.[76] Sun et al[77] documented production of TNF-α, IL-1β, and IL-6 by astrocytes in the spinal cords of mice that were chronically infected with MHV-JHM, localized to areas of virus infection and demyelination. TNF-α and IL-6 are also produced in the brains of acutely infected mice, but the major cell producing these cytokines is the macrophage. These cytokines may help recruit T-cells and monocytes and may increase vascular permeability.[78] IL-1β promotes leukocyte adhesion to endothelial cells, and TNF-α is toxic to oligodendrocytes.[63] The role of IL-6 is unclear. Effects attributed to IL-6 include recruitment and activation of T-cells and macrophages, expansion of CTLs, modulation of plasma cell differentiation, increased vascular permeability, downregulation of acute phase proteins, and contributions to immune-mediated destruction in the CNS.[79–82]

In a study of cytokine profiles in lethally compared to sublethally affected mice with JHM, both TH_1- and TH_2-type cytokines, including IFN-γ, IL-4, and IL-10, were induced in all mice.[83] In the mice that died, TNF-α was induced more rapidly, and IL-1α was increased. In mice with nonlethal infections, IL-12 and IL-1β were increased, and IL-6 was expressed early. Minor differences were observed in the patterns of inflammation in IL-10–deficient compared to syngeneic mice, but the outcome of infection (eg, mortality and virus load) was not affected.[84] These results, combined with those of Sun et al,[77] suggest that IL-1β may allow mice to survive the early stages of the disease but may not allow for clearance of chronic infection.

Interferon-γ also appears to be important for clearance of MHV infection. IFN-γ–deficient mice developed persistent JHM infection with increased clinical signs and mortality compared to mice competent to produce IFN-γ.[85] Antiviral antibody and CTL responses were normal in IFN-γ–negative mice, despite the fact that IFN-γ modulates antibody production. Viral antigen occurred in oligodendrocytes and in association with CD8+ T-cells, suggesting that IFN-γ is necessary for control of viral replication in oligodendrocytes. Treatment of mice with anti-IFN-γ antibody increased the mortality rate of mice, whereas immunotherapy with IFN-γ reduced mortality and virus load.[86]

MHV-OBLV60 infection in immunocompetent mice induced transient mRNA upregulation for cytokines IL-1α, IL-1β, IL-6, TNF-α, and IFN-γ.[25] Nude mice differed in their cytokine profiles in that they lacked mRNA for IFN-γ, whereas concentrations of the other cytokines remained persistently high. The authors suggested that the increased cytokines in the nude mice were produced by CNS glial cells and possibly CD4+ and CD8+ subsets. IFN-γ treatment of human neuronal cell cultures markedly increased the susceptibility of cells to infection with HCV-OC43 (although cells were susceptible to 229E without IFN-γ treatment).[87] In this study, the hypothesized role of IFN-γ was induction of MHC class I expression. IFN-γ may increase superoxide dismutase and protect against oxygen radicals, kill virus directly, and increase the cytotoxicity of other effector cells.

The chemokine CRG-2 is expressed primarily by astrocytes during MHV infection and co-localizes with areas of viral RNA and demyelination.[88] The function of CRG-2 is not known, but this chemokine is also found in simian immunodeficiency viral (SIV) encephalitis[89] and lymphocytic choriomeningitis.[90]

Prospects for Immunomodulation of FIP with Insight from the Mouse Model

With very little information available about the immunopathogenesis of neurologic FIP, research performed in mice can be used as a model for FIP and to contrast findings from the MHV model with those in FIP. The immunopathogenic mechanisms are expected to have important similarities, but the demyelination that occurs in MHV is a more extensive pathological sequela of coronaviral infection (but not more fatal for the patient) than the focal granulomas that occur in FIP. It can be hypothesized that in FIP, upregulation of cytokines IL-1β, IL-6, IFN-γ, and TNF-α may be important in mediation of destructive inflammation, but cytokines IL-6 and IFN-γ may be important in controlling viral infection, despite adverse inflammatory effects. Cytokine and chemokine alterations in the brains of mice and cats with coronavirus infections may provide valuable clues to the immunopathogenesis of these diseases, as well as possible diagnostic markers and targets for immunological treatment of disease.

It is tempting to consider cytokine modulation in the treatment of FIP, but this application is premature without information regarding the cytokine profiles of affected cats. In addition to characterizing the concentrations of cytokines in the CNS of cats with FIP, it will be important to describe the timing of upregulated cytokine transcription. In mice with HMV-JHM, treatment with recombinant IFN-γ resulted in reduced virus load in the liver but not in the brain.[86] If specific pro-inflammatory cytokines are found to be consistently high in cats with neurological FIP, use of cytokine antagonists may eventually be of benefit in treatment.

Successful management of FIP may consist of better methods of prevention as well as management of disease once it occurs. A commercial FIP vaccine is available that consists of a mucosally delivered, temperature-sensitive mutant form of FIPV. The vaccine virus is supposed to undergo replication only in outer oronasal cavities at low temperatures, thus triggering protective antibodies but not FIP. A few controversial studies have documented reduction in FIP as a result of vaccination.[91,92] Many vaccinated cats, however, fail to seroconvert with either IgG or IgA (Foley and Pedersen, unpublished data), and independent studies failed to identify vaccine efficacy.[93,94] Other vaccines, including DNA vaccines, have not progressed beyond experimental stages either because of lack of seroconversion, lack of protection, or both. In contrast with FIP vaccines, vaccines against MHV have been shown to protect mice from challenge with virulent virus. A vaccine with purified spike protein[95] and synthetic S2 led to neutralizing antibodies in vivo.[96,97] Recombinant subunits against S in tobacco mosaic virus were given subcutaneously or intranasally and were protective against MHV-JHM.[98]

The current standard of care for immunomodulation of FIP is immunosuppressive doses of prednisone, to sustain an acceptable quality of life for as long as possible. The effects of steroids include lymphocytolysis, inhibition of arachidonic acid metabolism, reduction in cytokine RNA transcription, and nitric oxide synthesis inhibition.[99] Other potentially useful anti-inflammatory drugs include antileukocyte antibodies and antioxidants. These treatments are only palliative. A better understanding of the fundamental pathogenesis of FIP will be necessary to offer better treatment and, ultimately, cure of this disease.

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